II. REMARKS

Summary Of Record Of Interview

A personal interview was held on October 29, 2004, between the examiner, Shengjun Wang, the applicant, Professor Mark Pepys, and the applicant's representatives, Thomas Cawley, Jr., and Charles Rories. Prior to the interview, a draft version of the present amendment and copies of the six cited references were provided to the examiner.

During the course of the interview, the applicant explained that at the time the present application was filed, persons of ordinary skill in the art recognized that the physiological activity of CRP in inflammatory and tissue-damaging conditions was not understood and could not be predicted. The applicant discussed the significance of two references that were co-authored by the authors of the cited prior art reference (Bhakdi et al.) in illustrating the lack of understanding of the physiological role of CRP in responses associated with inflammatory and tissue-damaging conditions such as atherogenesis by persons of ordinary skill in the art at the time of filing. In view of the general lack of understanding of the role of CRP in inflammatory and tissue-damaging conditions at the time of filing, the hypothesis of a pathological role of CRP in atherogenesis stated in the prior art reference would not have accepted as true by persons of ordinary skill in the art, in view of the complete absence of any supporting experimental evidence. The applicant explained that **his own studies of the role of CRP in experimental myocardial infarction, which are disclosed in the present application, are the first substantive experimental evidence that CRP has a causative role in injuries associated with inflammatory and tissue-damaging conditions**. The applicant also provided the examiner with a copy of his recently published scientific article that shows that CRP also has a causative role in injuries associated with cerebral infarct (Gill et al., J. Cerebral Blood Flow & Metabolism, November 2004, 24(11):1214-1218; copy attached).

The applicant and his representatives stated that the secondary references cited in the office action would not have corrected the defects of the Bhakdi et al. (1999) reference, and pointed out one of ordinary skill in the art would not have expected the unoxidized phosphatidylcholine phospholipid molecules described in the Yedgar and Wissner patents to be bound successfully as ligands by CRP. The examiner agreed to give full consideration to

the applicant's arguments. The examiner also suggested that the claims be amended to provide additional chemical description of the administered compound.

The applicant and his representatives greatly appreciate the examiner's willingness to hold the interview and to consider the applicant's proposed amendments and arguments for withdrawal of the outstanding rejections.

Preliminary Remarks:

Claims 1-25 and 39-56 are pending.

Claims 1, 16-18, and 56 are amended to be directed to the disclosed therapeutic method which comprises administering to the subject an effective amount of a compound capable of inhibiting the binding of C-reactive protein (CRP) to an autologous or extrinsic ligand thereof, wherein the compound comprises phosphocholine or a derivative thereof and binds to the calcium-dependent ligand binding site of CRP so as to interfere with binding of CRP to the autologous or extrinsic ligand thereof. Support for the amendment is found in the specification; for example, on pages 12-14, which describe practicing the claimed invention with a compound that comprises a phosphocholine derivative, and in original claim 10, which is expressly directed to a such a compound.

Patentability Remarks:

35 U.S.C. §112, First Paragraph

Claims 1-9, 16-19, 39-41, 44-46, 49, 55, and 56 were rejected under 35 U.S.C. §112, First Paragraph, because the specification allegedly does not enable a person skilled in the art to practice the claimed invention without undue experimentation. The applicants respectfully traverse this rejection. The independent claims have been amended to specify that the compound that is administered is one that comprises phosphocholine or a derivative thereof and binds to the calcium-dependent ligand binding site of CRP and interferes with the binding of CRP to an autologous or extrinsic ligand, as described, for example, on page 17 (lines 22-26). At the time the application was filed, the calcium-dependent ligand binding site of CRP was known to bind to multiple ligands, such as phosphocholine, phosphoethanolamine, and other phosphate monoesters. At the time of filing, skilled persons would therefore have been

able to identify compounds that comprise phosphocholine or a phosphocholine derivative and bind to the calcium-dependent ligand binding site of CRP and are suitable for the claimed invention without undue experimentation, using known, routine methods, such as screening and competition assays, as described on, for example, on pages 10-12 and 17 of the present application. Withdrawal of the rejection of claims 1-9, 16-19, 39-41, 44-46, 49, 55, and 56 under 35 U.S.C. §112, First Paragraph, is respectfully requested.

35 U.S.C. §103(a)

Claims 1-25 and 42-56 were rejected under 35 U.S.C. §103(a) as being obvious in view of Bhakdi et al. and Kitao et al., further in view of Yedgar et al. (U.S. Patent No. 5,064,817, "the Yedgar patent"), and further in view of Wissner et al. (U.S. Patent No. 4,640,913, "the Wissner patent"). The applicants respectfully traverse this rejection. **Prior to the discovery of the invention disclosed in the present application, persons of ordinary skill in the art did not know and could not have predicted that CRP actually has a causative role in the injuries to tissue associated with inflammatory and tissue-damaging conditions.**

Bhakdi et al. (1999) observed that CRP co-localizes with complement C5b-9 in atherosclerotic lesions, and reported that (i) CRP also co-localizes with enzymatically degraded LDL (E-LDL) in atherosclerotic lesions, (ii) CRP binds to E-LDL, (iii) CRP appears to enhance the ability of enzymatically degraded LDL (E-LDL) to activate complement in serum, and (iv) the binding of CRP to E-LDL is inhibited by phosphocholine. In view of the apposition of CRP, C5b-9, and E-LDL in atherosclerotic lesions, the reference proposed the hypothesis that accumulation of CRP in the lesions "may promote pathological events via complement activation." See the paragraph bridging page 2353.

One of ordinary skill in the art at the time the application was filed would not reasonably have expected that inhibition of the binding of CRP to its ligand at the site of an atherosclerotic lesion would provide therapeutic benefit, based on the teachings of the Bhakdi *et al.* reference. At the time the application was filed, CRP was known to augment complement activation at the site of tissue injury; however, CRP was also known to protect the tissue from assembly of terminal complement components, as described in Gershov et al.

(IDS ref. MMR). In fact, **at the time of filing, most persons of ordinary skill in the art considered CRP to have physiological activities that are beneficial for health**, as taught by Kilpatrick et al. and Steel et al., as discussed in the previous response. Therefore, one of skill in the art would not have regarded the observation by Bhakdi et al. that CRP, C5b-9, and E-LDL are all present in atherosclerotic lesions as evidence that was sufficient to support a conclusion that CRP has a causative role in the associated tissue damage.

The skepticism that would be shown by persons of skill in the art is further evidenced by two recently published articles of Bhakdi et al. ("Possible Protective Role for C-Reactive Protein in Atherogenesis," Circulation, 2004a, 109:1870-1876; and "Beyond cholesterol: the enigma of atherosclerosis revisited," Thromb. Haemost., 2004b, 91:639-645, copies attached), **which conclude that CRP may have a protective role in atherogenesis.** These references are co-authored by authors of the Bhakdi et al. (1999) reference that was cited as prior art. The first of these references (Bhakdi et al., 2004a) reports that binding of CRP to E-LDL in an atherosclerotic lesion triggers complement activation, but that the pathway is halted before the terminal sequence, as was previously observed by Gershov at al. (IDS ref. MMR) in a different system. Moreover, Bhakdi et al. (2004a) reports that CRP-dependent complement activation inefficiently generates C5b-9, and that it is essential to use a buffer such as VSB buffer in performing experiments to assay complement activation, as "many other buffers accelerate spontaneous C3 turnover and thus create artifacts." See the paragraph bridging pages 1873-4. The studies of complement activation reported in the Bhakdi et al. (1999) reference that was cited as prior art did not use VSB buffer, and so were presumably subject to such artifacts. **The Bhakdi et al. (2004a) reference states that the experimental data suggest that CRP has a protective role in atherogenesis (p. 1874, right column), and is clearly a retraction of the hypothetical proposal stated in the Bhakdi et al. (1999) reference that was cited as prior art.** The hypothesis of a protective role for CRP in atherogenesis is also described with detail in the above-identified review article by Bhakdi et al. (2004b). The complete reversal of opinion of Bhakdi et al. regarding the role of CRP in atherogenesis clearly illustrates the complexities and pitfalls of research in this area. The ambiguous and controversial aspects of research in the field, which have fostered confusion and uncertainty regarding the role of CRP in injuries to tissue associated with atherogenesis, were recognized by persons of ordinary skill in the art at the time the application was filed. In

view of the absence of supporting experimental data, one of ordinary skill in the art would therefore have been highly skeptical of the hypothesis of the cited Bhakdi et al. (1999), and would have continued to regard the role of CRP in injuries to tissue associated with atherogenesis as being undetermined and unpredictable at the time of filing.

The secondary references do not remedy the deficiencies of the 1999 Bhakdi et al. reference. Kitao reported the well-known finding that phosphocholine inhibits the calcium-dependent binding of CRP to LDL *in vitro*; and the Yedgar and Wissner patents taught the use of phosphocholine derivatives that inhibit PLA_2 and treat hypertension, respectively. As discussed in the previous response, the present application is concerned with the treatment of a tissue damaging condition and not with drugs that inhibit PLA_2 or have antihypertensive action. Any connection between the Yedgar and Wissner patents and either Bhakdi et al. or Kitao appears to arise solely as a result of a hindsight reconstruction of the present invention. Moreover, a person practicing the method of the Yedgar or the Wissner patent would not have been expected to practice the presently claimed method.

With respect to administering a PLA_2 inhibitor, Vadas et al. taught that CRP inhibits the activity of PLA_2 in a dose-dependent manner by a mechanism mediated by the calcium-dependent ligand binding site of CRP (for example, see "Inhibition of human group II phospholipase A_2 by C-reactive protein in vitro," J. Lipid Mediat. Cell Signal., 1995, 11(2):187-200, abstract attached). Vadas et al. therefore taught away from administering a PLA_2 inhibitor that also inhibits the calcium-dependent ligand binding activity of CRP. At the time the application was filed, one of ordinary skill in the art who sought to inhibit PLA_2 in a patient as taught by Yedgar et al. would reasonably have selected and used a PLA_2 inhibitor that does not also inhibit the calcium-dependent ligand binding activity of CRP, so that the patient could benefit from the PLA_2–inhibitory activity of CRP.

In addition, the phosphocholine derivatives disclosed in the Yedgar and Wissner patents comprise saturated, unoxidized alkyl chains such as are present in phosphatidylcholine choline. Tsujimoto et al. (J. Biochem. (Tokyo), 1980, 87(5):1531-7 abstract attached) and Mori et al. (Cell Mol Biol. 1991, 37(4):421-31, abstract attached) taught that such phospholipids are not bound effectively as ligands by CRP. The observation that CRP binds to oxidized but not unoxidized phosphocholine-containing phospholipid was

further corroborated after the filing date by Chang et al. See "C-reactive protein binds to both oxidized LDL and apoptotic cells through recognition of a common ligand: Phosphocholine of oxidized phospholipids," Proc Natl Acad Sci U.S.A., 2002, 99(20):13043-8, p. 13045; copy attached. Accordingly, one of ordinary skill in the art who practiced the methods of the Yedgar or Wissner patents would not have been expected to practice the claimed method, comprising administering a compound capable of inhibiting the binding of the calcium-dependent ligand binding site of CRP to an autologous or extrinsic ligand thereof.

The contribution made by the present inventor resides in a recognition that, in contrast to the prevailing common general knowledge at the time the invention was made, CRP markedly enhances tissue damage in an *in vivo* experiment involving acute myocardial infarction. This work clearly and definitively identifies CRP as a therapeutic target based on the first demonstration that human CRP actually causes increased tissue damage *in vivo* in a subject having an inflammatory/tissue-damaging condition. Contrary to the prevailing general knowledge, **the present invention comprises the first clear, direct demonstration of CRP causing more severe tissue damage than would have occurred in its absence,** with adverse clinical consequences *in vivo* both in myocardial infarction and cerebral infarction. The present invention thereby validates for the first time the inhibition of CRP binding to its ligands as a therapeutic strategy. Accordingly, while the prevailing common general knowledge indicated that inhibition of CRP ligand binding activity should be harmful, the present inventor has demonstrated that such inhibition would be useful in a method of treating or preventing tissue damage in a subject having an inflammatory and/or tissue damaging condition.

The claimed invention is based on an unexpected finding and is submitted to be ground-breaking work. The present application demonstrates *in vivo* that CRP is a pathogenetic factor causing tissue damage and provides a range of inhibitors for treating or preventing such damage. As discussed above, the cited prior art references, taken in combination, would not have motivated one of skill in the art to administer a compound that inhibits the binding of CRP to its ligand to a subject with a reasonable expectation of successfully treating or preventing atherosclerosis and its complications in the subject. Prior to the pioneering discovery of the present application, one of skill in the art simply could not have predicted that administration of a compound capable of inhibiting the binding of CRP to

its ligand would successfully treat or prevent tissue damage in a subject having an inflammatory and/or tissue damaging condition such as atherosclerosis. Accordingly, the claimed method would not have been obvious to one of ordinary skill in the art in view of the cited references, and withdrawal of the rejection of the claims under 35 U.S.C. §103(a) is respectfully requested.

III. CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,
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